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10/588,778	12/03/2007	Hiide Yoshino	2006_1312A	4646

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
09/17/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/588,778	YOSHINO ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 page / 07/29/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on January 21, 2010.

Status of Claims

Amendment of claims 1, 8-9, and 13-14 and cancellation of claim 2 is acknowledged.

Claims 1 and 3-16 are currently pending and are the subject of this office action.

Claims 1 and 3-16 are presently under examination.

Priority

The present application is a 371 of PCT/JP05/001932 filed on 02/09/05, and claims priority to foreign application: JAPAN 2004-032420 filed on 02/09/2004 and JAPAN 2004-032421 filed on 02/09/2004.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment and/or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Prior Art: counterpart

WO 02/34264 is the PCT counterpart to US 6,933,310.

WO 02/34264 has a 102(b) date as a result of its May 2, 2002 publication date.

US 6,943,185 is prior art under U.S.C 102(e) as a result of its August 23, 2005 publication date.

Because WO 02/34264 and US 6,933,310 appear to have identical disclosures, and because the WO document was published in Japanese language designating the United States, the US Patent US US 6,933,310, which is the National Stage entry of WO 02/34264 is being used as a translation of WO 02/34264 PCT. As such, any reference hereinafter to column and line numbers will be based upon the US Patent, but should be interpreted as referring to the corresponding disclosure of the aforementioned PCT counterpart.

Claim Rejections - 35 USC § 103 (new Rejection not Necessitated by Amendment)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ikeda (WO 02/34264, cited by Applicant, which is the PCT counterpart to US 6,933,310, see above prior art counterpart, cited in prior office action).

Claims 1 abd 3-7 recite a method of treating amyotrophic lateral sclerosis (AML) or symptoms caused by amyotrophic lateral sclerosis and/or suppressing the progression thereof, which comprises administering to a patient in need thereof as an active ingredient: edaravone, under the condition that a drug holiday period of 1 day or more is provided once, twice or more during the period for treating the disease or suppressing the progression of the disease.

Claim 3 further limits claim 1, wherein the drug holiday period is provided after a drug administration period of about 7 to 14 days.

Claim 4 further limits claim 1, wherein a second subsequent drug administration period is about 5 to 14 days.

Claim 5 further limits claim 1, wherein the drug holiday period is about 14 to 16 days.

Claim 6 further limits claim 1, wherein the drug administration period and the drug administration period are each 14 days.

Claim 7 further limits claim 1, wherein a course consisting of an initial drug administration period of 14 days and a drug holiday period of 14 days is provided, followed by repetitions of the following combination of periods: drug administration period: 5 days per week for 2 weeks; and drug holiday period: 14 days.

For claims 1-7, Ikeda teaches a method of treating amyotrophic lateral sclerosis comprising the administration of 3-methyl-1-phenyl-2-pirazoline-5-on (edaravone) (see for example claims 1-5). Ikeda further teaches that the route of administration of the medicament is not particularly limited (see column 5, lines 10-14) and that the medicament can be administered directly to the patient preferably in the form of a pharmaceutical composition (see column 5, lines 15-21). The dose of the medicament can be selected according to various conditions including type of disease being treated, progress of the disease or degree of the symptoms, and age and weight of the patient (see column 5, lines 53-57).

Ikeda does not teach the specific dose regimens which includes holiday periods as disclosed in claims 1-7. However, it's within the capability of the ordinary artisan to determine a specific dose regimen for a particular patient (see underline statement by Ikeda above) and adjust dose regimens based on the observed clinical effectiveness, thus resulting in the practice of claims 1-7 with a reasonable expectation of success.

Claim 8 further limits claim 1, wherein the daily dose contains about 15 to 240 mg of edaravone.

Claim 9 further limits claim 1, wherein the daily dose contains about 60 mg of edaravone.

For claims 8 and 9, Ikeda further teaches a daily dosage of approximately 0.01 microgram/kg to 10 mg/kg for an adult by injection or drip, which translates into 0.0008 mg/day (0.01 microgram/kg/day x 80 kg for an adult) to 800 mg/day (10 mg/kg/day x 80 kg), which clearly overlap the dosage of claims 8 and 9. MPEP 2144.05 states: In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

Claim 10 further limits claim 1, wherein the administration is carried out once daily.

Claim 11, further limits claim 1, wherein the administration is a continuous administration.

Claim 12, further limits claim 11, wherein the continuous administration is intravenous infusion administration.

Claim 13 further limits claim 12, wherein the administration rate in the intravenous infusion administration is about 0.5 to 1 mg/minute.

Claim 14 further limits claim11, wherein the continuous administration is an administration form that is substantially equivalent to the intravenous infusion administration wherein the amount of ederavone is administered at 0.5 to 1 mg per minute.

For claims 10-14, Ikeda further teaches that: the dose of the medicament can be selected according to various conditions including type of disease being treated, progress of the disease or degree of the symptoms, and age and weight of the patient. In general approximately 0.01 microgram/kg to 10 mg/kg per day for an adult is administered by injection or drip (see column 5, lines 52-63). Ikeda also teaches that the route of administration is not particularly limited, and it can be administered orally or parenterally (for example, intravenous, intramuscular, hypodermic or intradermal injections, or inhalation) (see column 5, lines 10-14).

Ikeda does not teach a once daily or a continuous administration, however it's within the capability of the ordinary artisan to determine a specific mode of administration for a particular patient and adjust dosage amounts based on the observed clinical effectiveness, thus resulting in the practice of claims 10-14 with a reasonable expectation of success.

Claims 15 and 16 further limit claim 1, wherein certain symptoms caused by ALS like: decreased respiratory function, voice and speech disorders, dysphagia, or upper and lower extremity motor disorders are being treated.

For claims 15 and 16, Ikeda teaches that ALS often begins at middle age, and is a lethal intractable disease, in which the condition rapidly deteriorates from muscular atrophy and muscle weakness to, finally, death due to respiratory insufficiency or the like in a matter of a few years (see column 1, lines 28-34). Ikeda further teaches that ALS is a cryptogenic disease mainly characterized by muscular atrophy and

fasciculation. The initial symptoms mainly include hand weakness, dyskinesia in the digits and hands, and fasciculation in the upper limbs, And ALS can be classified into upper limb type, bulbar type, lower limb type and mixed type according to onset site. With any type of the disease, muscle groups of the whole body are impinged with the progress of the symptoms (see column 4, lines 27-38).

Comments related to the above rejection

In the previous office action (05/17/10) the Examiner withdrew the above 103 rejection based on data presented by Applicant on 01/21/10 and the 132 affidavit dated 02/03/10. The data, according to Applicant shows unexpected results for the dose regimen claimed.

However, a careful review of the claims and the data presented by Applicant shows that the data presented is not commensurate in scope with the claims.

MPEP 716.02(d) states: "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Claims were directed to a process for removing corrosion at "elevated temperatures" using a certain ion exchange resin (with the exception of claim 8 which recited a temperature in excess of 100C). Appellant demonstrated unexpected results via comparative tests with the prior art ion

exchange resin at 110C and 130C. The court affirmed the rejection of claims 1-7 and 9-10 because the term "elevated temperatures" encompassed temperatures as low as 60C where the prior art ion exchange resin was known to perform well. The rejection of claim 8, directed to a temperature in excess of 100C, was reversed.). See also *In re Peterson*, 315 F.3d 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003) (data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims.)."

Although Applicant was able to demonstrate unexpected results for the particular dose regimen disclosed in the 1.132 declaration dated 02/03/10 (drug administered for two days with a holiday period of two days, then two days of drug administration followed by two holiday days). However this narrow set of data can not be extrapolated to other dose regimens wherein for example the administration of ederavone is given for 100 consecutive days followed by one or two drug holiday periods. In other words, the data provided by Applicant in the specification and in the 1.132 declaration is not commensurate is scope with the claims.

Withdrawn Rejections and/or Objections

Claims rejected under 35 USC 112, first paragraph (scope of enablement).

Due to applicant's amendments, the scope of enablement rejection is now moot.

Rejection under 35 USC 112, first paragraph (scope of enablement) is withdrawn.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1628.
September 2, 2010